Each of the objections and rejections levied in the Office Action is addressed individually below is they pertain to the remaining claims as amended.

Support for the Amendments

Support for the structural limitations of claims 1, 7, 16, 18, and 25 can be found at page 10 line 21 to page 11, line 13; and page 12, lines 8-16. Support for the functional limitations of claims 1, 2, 10, 16, and 18 can be found at page 10, lines 8-14.

Information Disclosure Statement

The Examiner states that the lined through references on the Applicant's information disclosure statement, filed December 14, 1998, fail to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP §609, because they fail to include a complete citation of the references. Applicants apologize for this oversight and submit herewith complete citation information for the lined through references, copies thereof, and a substitute IDS.

Sequence Listing

The disclosure stands objected to because the sequences disclosed on page 22, lines 22 and 24, of the specification lack SEQ ID NOS. Applicants have amended the specification to include SEQ ID NOS at page 22, lines 22 and 24. In addition, Applicants

submit herewith a new Sequence Listing and Statement under 37 CFR 1.825 that assigns the sequences at page 22, lines 22 and 24 SEQ ID NOS: 17 and 18. Withdrawal of this objection is requested.

Objection under 1.821(d)

The Examiner objected to claims 1, 3, 16, and 18 for not complying with 1.821(d) of the Sequence Rules and Regulations because when the claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing," reference must be made to the sequence by use of the assigned identifier in the claims of the application. Applicants submit that the appropriate sequence identifiers have been added to claims 1, 16, and 18. Claim 3 has been canceled by the above amendment. Withdrawal of this objection is now requested.

Objection Under 37 CFR 1.75(c)

The Examiner objected to claim 3 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have canceled claim 3 and thus request withdrawal of this objection.

Rejections under 35 U.S.C. § 101

Claims 16 and 17 stand rejected under 35 U.S.C. § 101 because the claims are

directed to non-statutory subject matter. Specifically, the Examiner states that absent a claim limitation such as "isolated" or "purified," the cells as claimed have the same characteristics as naturally occurring cells, *in situ* in *C. elegans*. Accordingly, Applicants have amended claim 16, from which claim 17 depends, to recite a cell which contains a "substantially pure" nucleic acid encoding the LIN-37 polypeptide. Support for this amendment can be found at page 12, lines 8-16, where the term "substantially pure" is defined. In light of this amendment, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-7, 10-18, and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. This rejection has several aspects that are addressed individually below.

The Examiner states that claims 1, 3, 7, 10, 16, and 18 are vague and indefinite in that they are drawn to non-elected inventions (LIN-35, LIN-55, LIN-53, LIN-52, LIN-54, E2F-1, SEQ ID NO:3-16). Applicants have canceled claim 3 and amended claims 1, 7, 10, 16, and 18 to recite only LIN-37. In light of these amendments, withdrawal of this rejection is requested.

The Examiner states that claims 1, 3, 16, and 18 are vague and indefinite in the recitation of "LIN-37." Applicants have canceled claim 3 and amended claims 1, 16, and 18 to recite "a LIN-37 polypeptide having about 50% or greater amino acid sequence

identity to SEQ ID NO:1." In light of these amendments, withdrawal of this rejection is requested.

The Examiner states that claim 10 is vague and indefinite in the recitation of "having about 50% or greater nucleotide sequence identity to." In response, Applicants point out that the meaning of this phrase is defined in detail in the specification at page 10, line 21 to page 13, line 4. The specification also provides specific sequence analysis software with default settings that can routinely be used to measure sequence identity. In light of these teachings, withdrawal of this rejection is requested.

The Examiner states that claim 25 is vague and indefinite in the recitation of "SynMuv gene." In response, claim 25 has been amended to recite "a *lin-37* nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO:2." In light of this amendment, withdrawal of the rejection to claim 25 is requested.

The Examiner states that the recitation of "cell proliferation disease" in claim 17 is vague and indefinite. The Examiner states that the metes and bounds of what qualifies as a "cell proliferation disease" is unclear. In response, Applicants have amended claim 17 recite "a cell being present in a patient having a condition involving altered cell proliferation." Support for this amendment can be found in the section entitled "Detection of a Condition Involving Altered Cell Proliferation" at page 33, line 21 to page 34, line 2, which states,

> "SynMuv polypeptides and nucleic acid sequences find

> diagnostic use in the detection or monitoring of conditions involving aberrant levels of cell proliferation. A decrease or increase in the level of SynMuv production may provide an indication of a deleterious condition. Levels of SynMuv expression may be assayed by any standard technique."

In addition, the phrase "altering cell proliferation" is defined at page 10, lines 8-14. Pages 34-36 continue to teach a variety of methods by which cells from a patient may be analyzed to detect a condition involving altered cell proliferation. One skilled in the art would understand that a patient having a condition involving altered cell proliferation would mean a patient having a condition involving insufficient cell proliferation, e.g., insufficient hair follicle development (baldness), or a condition involving excessive cell proliferation, e.g., cancer. In light of the amendment to claim 17 and the remarks provided herein-above, withdrawal of this objection is requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-6, 11-18, and 25 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection has several aspects which are addressed below in the order they appear in the Office Action.

First, the Examiner states that claim 25 is broadly drawn to a "gene," but the specification describes only the DNA sequences of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14,

and 15. In addition, the Examiner states that the specification does not describe any of the structural elements of a gene that encodes these various cDNA sequences.

Applicants point out that claim 25 has been amended to recite a substantially pure *lin-37* nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO:2 isolated according to the method comprising: (a) providing a cell sample; (b) introducing by transformation into the cell sample a candidate *lin-37* nucleic acid; (c) expressing the candidate *lin-37* nucleic acid within the cell sample; and (d) determining whether the cell sample exhibits an altered cell proliferation response, whereby an altered level of cell proliferation identifies a *lin-37* nucleic acid.

Amended claim 25 now clearly sets forth specific *lin-37* nucleic acids "having about 50% or greater nucleotide sequence identity to SEQ ID NO:2." The term "substantially pure" is defined in the specification, with respect to DNA, as DNA that is

> "free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence" (page 12, lines 8-16).

Sequence identity, such as used in the phrase "about 50% or greater nucleotide sequence identity" is clearly defined in the specification at page 10, line 21, to page 11, line 4,

which states,

> By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% homology to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably 110 nucleotides."

Thus, Applicants assert that the written description fully supports claim 25, as amended herein. Withdrawal of the rejection to claim 25 is requested.

The Examiner further states that claims 1, 3, 16, and 18 are broadly drawn to nucleic acid molecules encoding a SynMuv polypeptide "LIN-37," and claim 25 is broadly drawn to "SynMuv" genes, but the specification teaches only the cDNA sequence (SEQ ID NO:2) that encodes the LIN-37 polypeptide (SEQ ID NO:1) in *C. elegans*. In addition, the Examiner states that the instant specification, which sets forth only one specific cDNA sequence for LIN-37, obtained from *C. elegans*, does not provide an adequate written description for the DNA molecules as broadly as claimed from any source.

Claim 3 has been canceled, and claims 1, 16, and 18 have been amended to point out the extent or type of sequence and functional relationship that the claimed nucleic acids must have. Specifically, claims 1, 16, and 18 now recite nucleic acids encoding

LIN-37 polypeptides, wherein the polypeptides share about 50% or greater amino acid sequence identity to SEQ ID NO:1 and wherein the polypeptides are capable of altering cell proliferation. Support for the phrase "about 50% or greater amino acid sequence identity" can be found at page 10, line 21 to page 11, line 4, as cited above. Support for the phrase "wherein the polypeptides are capable of altering cell proliferation" can be found at page 10, lines 8-14, which define the phrase "altering cell proliferation" as "increasing or decreasing the number of cells which undergo cell division in a given cell population or altering the fate of a given cell." Further support for "altering cell proliferation" can be found at page 9, lines 10-15, which states that a SynMuv gene family member, i.e., lin-37, encodes "a polypeptide which modulates cell death (inhibiting or enhancing) in a cell or tissue when provided by other intracellular or extracellular delivery methods."

In light of the present amendments, Applicants assert that the specification provides an adequate written description for the nucleic acids now claimed. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-6, 11-18, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claims. Specifically, the Examiner states that absent claim limitations

directed at further functional or physical properties of LIN-37, one of skill in the art can not make and use any LIN-37 other than the one encoded by SEQ ID NO:2.

Applicants have canceled claim 3, and amended claims 1, 16, 18, and 25 to point out the extent or type of functional and physical properties that the claimed nucleic acids must have. First, as pointed out above, claims 1, 16, 18, and 25 now recite nucleic acids encoding LIN-37 polypeptides, wherein the polypeptides share about 50% or greater amino acid sequence identity to SEQ ID NO:1. Moreover, claims 1, 16, 18, and 25 have been amended to include an additional functional limitation that clearly sets forth that the nucleic acids of claims 1, 16, 18, and 25 must encode polypeptides capable of altering cell proliferation.

Structure and Function of lin-37 Genes

The specification clearly defines a relationship between the structure of the *lin-37* gene and the function of the LIN-37 polypeptide and points out that additional *lin-37* genes may be identified using these characteristics in combination. The specification teaches that a conservation in structure is important for a conservation in function of a particular gene. For example, at page 9, lines 10-15, the specification states that

> "By 'SynMuv gene' is meant a gene encoding a polypeptide which modulates cell death (inhibiting or enhancing) in a cell or tissue when provided by other intracellular or extracellular delivery methods. In preferred embodiments the SynMuv gene is a gene having about 50%

> or greater nucleotide sequence identity to at least one of the SynMuv amino acid encoding sequences of Figs. 2, 4, 6, 8, 9, 11, or 13 or encoded by the sequence of Fig. 26 or Fig. 27, or portions thereof.
>
> By an 'SynMuv gene' is also meant any member of the family of genes characterized by their ability to modulate cell proliferation and having at least 10%, preferably 30%, and most preferably 50% amino acid sequence identity to at least one of the SynMuv protein described herein below. Representative members of the SynMuv gene family include, the *lin-37,* lin-*35, lin-53, lin-55, lin-52, lin-54,* and E2F-1 gene of *C. elegans*, and the *lin-54* genes of the mouse and human."

Based on these statements, it is clear that the specification further recognizes that these structural and functional characteristics can be used to identify additional *lin-37* genes in other species. As but another example, Applicants point out that, the specification states that

> "Experiments which stem directly from this research include searches for mammalian homologs of the novel SynMuv genes. Such homologs may function in activating, enhancing, or otherwise intensifying the effects of tumor suppressors or oncogenes in mammals" (page 19, lines 3-6).

Thus, the specification clearly sets forth a strategy for identifying *lin-37*-related genes.

The specification teaches a repeatable process by which *lin-37* genes and mutants thereof are identified. In order to achieve this, the specification teaches that one may, 1) identify a nucleic acid having structural similarity to at least a portion of a *lin-37* gene or *lin-37* gene mutant; and 2) test the function of the putative *lin-37* gene or *lin-37* gene mutant. Both the structural and functional characteristics of the *lin-37* gene and protein

are described in detail in the specification.

Structure of a lin-37 Gene

The specification provides the sequence of the *lin-37* gene and the encoded polypeptide. In addition, as described above, the specification clearly defines what is meant by a gene that encodes a polypeptide having "about 50% or greater amino acid sequence identity" to LIN-37 and teaches how one of ordinary skill in the art might identify such a sequence. The specification even provides teachings of a standard sequence analysis software package (page 10, line 21 to page 11 line 13) that can be used to calculate the sequence identity of LIN-37 to any given amino acid (or nucleic acid) sequence. Specifically, the specification provides sequence analysis software program (Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705) with default settings that can be used to identify nucleic acids having 50% or greater identify to SEQ ID NO:2. For example, at page 11, lines 5-13, the specification states that

> "Sequence identity may be measured using sequence analysis software on the default setting (i.e., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). Such software may match similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine, valine,

isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine."

In light of these teachings, Applicants submit that any person skilled in the art of gene cloning would be able to identify a sequence having about 50% or greater nucleotide sequence identity to a given sequence, particularly the *lin-37* gene sequence. One of ordinary skill in the art would recognize that the sequence analysis software program described in the specification (or variations thereof), with the default settings provided, could be used to identify additional *lin-37* genes and gene mutants. As stated in the specification, this may be accomplished by matching similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications (page 11, lines 8-10). These teachings make it clear that a gene encoding a protein having about 50% or greater amino acid identity to LIN-37, according to a standard sequence analysis software package, classifies as a *lin-37* gene according to the invention.

Function of a lin-37 Gene

With respect to step 2), testing the function of a putative *lin-37* gene or *lin-37* gene mutant, the specification sets forth that in addition to "having about 50% or greater nucleotide sequence identity" to an SynMuv family member gene, of which *lin-37* is a member, the *lin-37* gene may also encode a "polypeptide which modulates cell death (inhibiting or enhancing) in a cell or tissue when provided by other intracellular or

extracellular delivery methods" (page 9, lines 10-15). As described above, the specification defines the phrase "modulating cell proliferation" or "altering cell proliferation" to mean, "increasing or decreasing the number of cells which undergo cell division in a given cell population or altering the fate of a given cell" (page 10, lines 8-10). The specification proceeds to teach that "[i]t will be appreciated that the degree of modulation provided by a SynMuv or modulating compound in a given assay will vary, but that one skilled in the art can determine the statistically significant change in the level of cell proliferation which identifies a SynMuv or a compound which modulates a SynMuv" (page 10, lines 10-14). Thus, the phrase "able to alter cell proliferation" used in the claims encompasses these definitions.

The specification demonstrates identification the SynMuv gene family and suggests that additional gene family members, having functional similarity, may be easily identified. For example, the specification states that "[e]xperiments which stem directly from this research include searches for mammalian homologs of the novel SynMuv genes" (page 19, lines 3-4). The specification further states that "[s]uch homologs may function in activating, enhancing, or otherwise intensifying the effects of tumor suppressors or oncogenes in mammals" (page 19, lines 3-6). Moreover, the specification suggests that "[g]enetic enhancer or suppressor screens may be performed to identify new genes which may function in/or initiating, enhancing, otherwise interfacing with this Rb-related pathway" (page 10, lines 6-9). Based on these teachings, one of ordinary skill in

the art would recognize that additional cell death genes may be routinely isolated from other organisms using the structural and functional characteristics of *lin-37* provided in the specification. Another aspect of this teaching is that these characteristics are similarly applicable to the identification of mutant cell death genes, as described in the specification (page 17, lines 4-7).

Identification of lin-37 Genes

Thus, the specification teaches that the full effectiveness of the strategy provided by the specification is realized when the structural and functional features of the *lin-37* gene are combined to identify additional *lin-37* genes or gene mutants. One aspect of this teaching is that these characteristics are applicable to the identification of *lin-37* genes in other organisms (e.g., mammals, preferably humans). Based on these teachings, one of ordinary skill in the art would recognize that additional cell death genes may be routinely isolated from other organisms using the structural and functional characteristics of *lin-37* provided in the specification. Another aspect of this teaching is that these characteristics are similarly applicable to the identification of mutant *lin-37* genes, as described in the specification.

Summary

In summary, the specification provides a strategy by which the structural and

functional characteristics of *lin-37* are used in combination to identify additional *lin-37* genes or gene mutants. First, the present invention provides a precise definition and specific parameters that can be employed to identify a gene that is structurally similar to *lin-37*. In addition, the specification teaches that a *lin-37* gene must further have the function of being able to alter cell proliferation. Given this information, the skilled artisan would appreciate that these findings can be used to identify additional nucleic acids related structurally and functionally to the *lin-37* nucleic acid described herein. In light of these teachings, Applicants submit that the claims are now commensurate in scope with the specification as filed. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 102(a)

Claims 1, 3, 5, 15, and 25 stand rejected under 35 U.S.C. § 102(a) as being anticipated by the June 1996 meeting abstract of Lu and Horvitz. The Examiner states that "Lu and Horvitz discloses a LIN-37 encoding nucleic acid, a vector containing said nucleic acid, and genes identified by a rescue method comprising transformation and screening for altered cell proliferation that are the same as that claimed." This rejection is respectfully traversed because the June 1996 meeting abstract of Lu and Horvitz does not constitute prior art under 35 U.S.C. § 102(a).

Specifically, Applicants note that the authors of the June 1996 meeting abstract are Xiaowei Lu and H. R. Horvitz, who are co-inventors of the present application.

Applicants also note that the June 1996 abstract was disclosed on June 9, 1996, that is, less than one year before the filing date of May 28, 1997 of provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit. Accordingly, because the June 1996 abstract was disclosed within one year of the Applicant's effective filing date - May 28, 1997 - and because Dr. Lu's and Dr. Horvitz's disclosure of their own work within the year before the effective filing date cannot be used against them under § 102(a), this reference does not qualify as prior art to the claimed invention. This basis for the § 102 rejection should be withdrawn. *In re Katz* 215 U.S.P.Q. 14 (C.C.P.A. 1982).

Claims 1, 3, and 5 stand rejected under 35 U.S.C. § 102(a) as being anticipated by the June 1996 meeting abstract of Ceol and Horvitz. The Examiner states that "Ceol and Horvitz discloses a cloned nucleic acid encoding the LIN-37 polypeptide that is the same as that claimed." This rejection is respectfully traversed because the June 1996 meeting abstract of Ceol and Horvitz does not constitute prior art under 35 U.S.C. § 102(a).

Specifically, Applicants note that the authors of the June 1996 meeting abstract are Craig Ceol and H. R. Horvitz, who are co-inventors of the present application. Applicants also note that the June 1996 abstract was disclosed on June 9, 1996, that is, less than one year before the filing date of May 28, 1997 of provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit. Accordingly,

because the June 1996 abstract was disclosed within one year of the Applicant's effective filing date - May 28, 1997 - and because Dr. Ceol's and Dr. Horvitz's disclosure of their own work within the year before the effective filing date cannot be used against them under § 102(a), this reference does not qualify as prior art to the claimed invention. This basis for the § 102 rejection should be withdrawn. *In re Katz* 215 U.S.P.Q. 14 (C.C.P.A. 1982).

Claims 1, 3, 5, 11, 14-16, and 18 stand rejected under 35 U.S.C. § 102(a) as being anticipated by the may 1997 meeting abstract of Lu and Horvitz. The Examiner states that "Lu and Horvitz discloses a LIN-37 encoding nucleic acid, including said nucleic acid linked to a cell type specific promoter (col-10) and vectors and cells (embryos) containing said nucleic acid that are the same as that claims." This rejection is respectfully traversed because the May 1997 meeting abstract of Lu and Horvitz does not constitute prior art under 35 U.S.C. § 102(a).

Specifically, Applicants note that the authors of the May 1997 meeting abstract are Xiaowei Lu and H. R. Horvitz, who are co-inventors of the present application. More importantly, Applicants also note that the May 1997 abstract was disclosed on May 28, 1997, that is, on the filing date of May 28, 1997 of provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit. Accordingly, because the May 1997 abstract was not disclosed before the day of the Applicant's effective filing date - May 28, 1997 - this reference does not qualify as prior art to the claimed invention.

This basis for the § 102 rejection should be withdrawn.

Claim 25 stands rejected under 35 U.S.C. § 102(a) as being anticipated by the May 1997 meeting abstract of Ceol and Horvitz. The Examiner states that "Ceol and Horvitz discloses genes identified by a method comprising 'providing a cell sample,' 'introducing by transformation into said cell sample a candidate SynMuv gene,' 'expressing said candidate SynMuv gene within said cell sample' and 'determining whether said cell sample exhibits an altered cell proliferation response' that is the same as that claimed." This rejection is respectfully traversed because the May 1997 meeting abstract of Ceol and Horvitz does not constitute prior art under 35 U.S.C. § 102(a).

Specifically, Applicants note that the authors of the May 1997 meeting abstract are Craig Ceol and H. R. Horvitz, who are co-inventors of the present application. More importantly, Applicants also note that the May 1997 abstract was disclosed on May 28, 1997, that is, on the filing date of May 28, 1997 of provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit. Accordingly, because the May 1997 abstract was not disclosed prior to the day of the Applicant's effective filing date - May 28, 1997 - this reference does not qualify as prior art to the claimed invention. This basis for the § 102 rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Claims 16 and 17 stand rejected under 35 U.S.C. § 102(b) as being anticipated by

Hedgecock (Genetics 141:989, 1995). Specifically, the Examiner states "Hedgecock discloses a cell (each of six cells 'called vulval precursor cells') which contains the nucleic acid encoding the LIN-37 polypeptide and is the same as that claimed (see p. 989, col.2)."

Claims 16 and 17 have been amended to recite a cell which contains a "substantially pure" nucleic acid encoding a LIN-37 polypeptide having about 50% or greater amino acid sequence identity to SEQ ID NO:1, wherein said polypeptide has the ability to alter cell proliferation. As defined in the specification the phrase "substantially pure" means:

> "DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences."

According to the above definition, "*lin-37*. . . defined by a mutation that affects *C. elegans* vulva development" as stated on page 989, col.2, of Hedgecock, does not classify as a substantially pure nucleic acid. The term "*lin-37*" as used by Hedgecock is used merely to refer to the phenotype displayed by nematodes carrying an, as yet, unidentified mutation in the *lin-37* gene. Furthermore, the *lin-37* gene of Hedgecock is not "free of

the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene" as required by the present claims. In light of these distinctions, this basis for the § 102 rejection should be withdrawn.

Claims 15-18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Maruyama (Gene 120:135, 1992). Specifically, the Examiner states that "Maruyama discloses a cell (*E. coli* cells containing a nematode cDNA library, see abstract) that is the same as that claimed in claims 16-18." The Examiner proceeds to state that within this library would be clones, in the vector λMGU2, that contain the cDNA encoding the LIN-37 polypeptide and are the same as the vector claimed in claim 15."

Applicants assert that the cells and vectors of Maruyama do not disclose the cells and vectors containing the "substantially pure" *lin-37* nucleic acid of the present invention, as now claimed. Maruyama disclose that the λMGU2 vector can accommodate an insert up to 10 kb in size (page 137, first column). It is highly unlikely that the *lin-37* nucleic acid contained by the λMGU2 vector is "free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene," as required by the present claims.

Moreover, Maruyama do not disclose purification of a single clone away from other cDNA clones of the cDNA library. One skilled in the art, absent knowledge of the *lin-37* gene sequence, would not be able to clone *lin-37*.

In light of these distinctions, this basis for the § 102 rejection should be

withdrawn.

Claims 1, 3, 5, 7, and 15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Accession Number U00047 (10 May 1994). The Examiner states that "Accession Number U00047 discloses a polynucleotide sequence that is the same as that claimed."

Applicants point out that, Accession Number U00047 discloses a "*Caenorhabditis elegans* cosmid ZK1418" as stated after "DEFINITION" in the sequence list. Furthermore, after "TITLE" is stated that the vector contains "2.2 Mb of contiguous nucleotide sequence from chromosome III of *C. elegans*." In addition, the NCBI (National Center for Biotechnology Information) database contains a listing of nine genes predicted from the ZK418 cosmid sequence. A page from this web site listing the nine ZK418 predicted sequences, T27855, T27854, T27853, T27852, T27851, T27850, T27849, T27856, and T27857 is submitted concurrently with the present response. In further support of these assertions, Applicants submit a page from the C. elegans database ACeDB (A C. elegans Database) with the present response. Applicants direct the Examiner's attention to the left side of the page which represents the "ZK418" cosmid. The nine genes that fall within the ZK418 cosmid (ZK418.1, ZK418.2, ZK418.3, ZK418.4, ZK418.5, ZK418.6, ZK418.7, ZK418.8, and ZK418.9) and their intron/exon structure are indicated to the right of '"K418." To the far right of the page is a listing of each predicted gene and a listing of cDNA clones, each with its own designation that

begins with "yk," that have been isolated for each gene. Based on these facts, it is clear that the *lin-37* gene sequence contained in cosmid ZK418, like the *lin-37* nucleic acids of Hedgecock and Maruyama, is not "free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene," as required by the present claims. In light of this distinction, this basis for the § 102 rejection should be withdrawn.

Lastly, claim 25 stands rejected under 35 U.S.C. 102(b) as being anticipated by pp. 296-297 of "*Basic Methods in Molecular Biology*" (1986). Specifically, the Examiner states that pages 296-297 disclose a gene identified by a method comprising 'providing a cell sample,' 'introducing by transformation into said cell sample a candidate SynMuv gene,' expressing said candidate SynMuv gene within said cell sample,' and 'determining whether said cell sample exhibits an altered cell proliferation response' that is the same as that claimed."

Claim 25 has been amended to recite a substantially pure *lin-37* nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO:2 isolated according to the method comprising: (a) providing a cell sample; (b) introducing by transformation into said cell sample a candidate *lin-37* nucleic acid; (c) expressing said candidate *lin-37* nucleic acid within said cell sample; and (d) determining whether said cell sample exhibits an altered cell proliferation response, whereby an altered level of cell proliferation identifies a *lin-37* nucleic acid.

Applicants point out that for a cited reference to anticipate a claim under § 102, the reference must teach every element of that claim (MPEP 2131). The reference, *"Basic Methods in Molecular Biology"* (1986), does not disclose a substantially pure *lin-37* nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO:2. Nor does this reference teach of a nucleic acid sequence that encodes a polypeptide capable of altering cell proliferation response when introduced by transformation into a cell.

In light of the above, it is clear that the cited reference, *"Basic Methods in Molecular Biology"* (1986), does not provide the sequence of the *lin-37* nucleic acids recited in claim 25. Thus, this reference cannot anticipate claim 25 and withdrawal of the rejection to claim 25 is requested.

Conclusion

In light of the above, Applicants assert that the claims should now be in condition for allowance. Enclosed is a petition to extend the period for replying for three months, to and including April 13, 2000. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 13, 2000

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